Osteoporosis International (2020) 31:1671–1682
https://doi.org/10.1007/s00198-020-05429-6

REVIEW

# Exposure to heavy metals and the risk of osteopenia or osteoporosis: a systematic review and meta-analysis

C. Jalili[1] · M. Kazemi[2] · E. Taheri[3,4] · H. Mohammadi[5] · B. Boozari[5] · A. Hadi[6] · S. Moradi[5]

Received: 26 March 2020 / Accepted: 22 April 2020 / Published online: 2 May 2020


## Abstract

The relationship between heavy metal exposure and risk of osteopenia or osteoporosis has biological plausibility, yet it remains inconclusive; therefore, we conducted a systematic review and meta-analysis to evaluate the associations between exposure to heavy metals (i.e., cadmium, lead, and mercury) and the risk of osteopenia or osteoporosis. Databases of MEDLINE, Embase, Scopus, and Web of Science were searched through November 2019, to identify studies that evaluated the relationship between exposure to cadmium, lead, and mercury and risk of osteopenia or osteoporosis in adults. Fourteen eligible studies were included. Effect sizes expressed as pooled odds ratios (OR) and 95% confidence intervals (CI) were estimated using weighted random-effect models. Exposure to cadmium (OR = 1.35; 95% CI: 1.17 to 1.56; $P \leq 0.001$) and lead (OR = 1.15; 95% CI: 1.00 to 1.32; $P = 0.05$) was associated with an increased risk of osteopenia or osteoporosis, unlike mercury. Subgroup analyses showed cadmium exposure increased the risk of osteopenia or osteoporosis in older (> 65 yrs.; OR = 1.43; 95%CI: 1.08 to 1.88, $P = 0.01$) compared with younger (18-65 yrs.; OR = 1.24; 95% CI: 1.02 to 1.52, $P = 0.03$) adults. Also, lead exposure increased the risk in men (OR = 1.55; 95% CI: 1.15 to 2.09, $P = 0.007$) unlike in women. By contrast to urinary levels, blood (OR = 1.26; 95% CI: 1.08 to 1.47, $P = 0.003$) and dietary (OR = 1.46; 95% CI: 1.28 to 1.67, $P < 0.001$) levels of cadmium were associated with an increased risk of osteopenia or osteoporosis. Exposure to cadmium and lead may be associated with an increased risk of osteopenia or osteoporosis, although high heterogeneity was detected.

**Keywords** Bone · Cadmium · Lead · Mercury · Musculoskeletal diseases · Transition elements

## Introduction

Osteoporosis is known as a "silent disease," in part, due to the progressive loss of bone mass without any specific symptoms until a fracture occurs. The fracture secondary to osteoporosis has major public health and economic consequences [1]. Increased morbidity rates, low quality of life, long hospital stays, staggering healthcare costs, and increased mortality rates associated with osteoporotic fractures have been established [2–4]. Identification of risk factors linked to the loss of bone mass is critical to prevent and manage the development of osteopenia and osteoporosis [4]. Previous studies have proposed certain risk factors associated with the development of osteopenia and/or osteoporosis, including female gender [5], menopause [1], genetic factors [6], aging [7], poor sleep patterns [3], low physical activity levels [8], poor diet quality [9], excessive alcohol intake [10], weight abnormality [11], stress [12], smoking [13], specific medications [14], and environmental exposure to heavy metals at high concentrations [15].

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00198-020-05429-6) contains supplementary material, which is available to authorized users.

✉ S. Moradi
sajadmoradi9096@gmail.com; s.moradi@mail.mui.ac.ir

[1] Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[2] Division of Nutritional Sciences, Human Metabolic Research Unit, Cornell University, Ithaca, NY, USA

[3] Environment Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

[4] Department of Environmental Health Engineering, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

[5] Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

[6] Halal Research Center of IRI, FDA, Tehran, Iran

Anthropogenic and geogenic sources have been proposed to affect exposure to heavy metals to hazardous levels [16]. Excessive amounts of heavy metals have been shown to enter the food chain system through the pollution of farmland soil and water [17]. Also, these metals can enter the human body via other environmental sources, including smoking and air pollution. However, there is no universal consensus about the definition of hazardous or safe limits of exposure to heavy metals, and their health consequences remain poorly elucidated [16]. Heavy metals can be accumulated in the body soft and hard tissues or organs and, therefore, exert adverse health effects [18]. Accordingly, previous studies have shown that the accumulation of heavy metals in bones aggravates bone resorption and alters bone mineral content, which is similar to the characteristics of osteoporosis and bone fracture [16]. Negative impacts of heavy metal exposure on bone health depend on the concentration, frequency, and duration of exposure and variability in biological species [19]. Several studies have shown the negative impacts of daily or long-time exposure to certain heavy metals, including cadmium, lead, and mercury, on bone health, at irreversible conditions in some cases even at low concentrations [20–23]; these observations may reflect the severity of toxicity and detrimental effects of cadmium, lead, and mercury on bone loss. Cadmium and mercury accumulate primarily in the liver and kidneys with low clearance rates due to inefficient urinary and biliary excretion rates [24]; by contrast, lead is quickly filtered and excreted via urine [24]. Cadmium directly interferes with calcium absorption, which is critical for maintaining bone health [24] and indirectly disrupts bone metabolism by decreasing vitamin D synthesis in kidneys secondary to interfering with the parathyroid hormone action, and reducing the intestinal absorption and increasing urinary excretion of calcium [25]. Also, lead has been shown to accelerate bone turnover and reduce bone mineralization and mineral density (BMD) [26]. Lead has a higher affinity for osteocalcin than calcium and competes with calcium for substitution in the structure of hydroxyapatite crystals, thereby altering bone microstructure [27, 28]. Besides, a previous study suggested that short-term exposure to mercury has a protective effect on osteoblasts by improving the expression of metallothionein [29]. By contrast, Suzuki et al. reported that mercury exposure was associated with low BMD by altering calcium homeostasis and osteoclast activation [30].

Taken together, the negative effects of exposure to cadmium, lead, and mercury on bone health has biological plausibility and may increase the likelihood of osteopenia or osteoporosis; however, current studies that evaluated the link between exposure to cadmium, lead, and mercury and the risk of osteopenia or osteoporosis have yielded inconsistent results. To our knowledge, no attempts have been made to summarize the associations between heavy metal exposure and bone health. Therefore, we conducted a systematic review and meta-analysis to evaluate the associations between exposure to cadmium, lead, and mercury and the risk of osteopenia or osteoporosis.

## Methods

### Literature search and selection

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. A systematic search and literature review were performed using the electronic databases PubMed MEDLINE, Scopus, Embase, and ISI Web of Science through November 30, 2019. The medical subject heading (MeSH) and key terms were used for a search line via MEDLINE as described herein: (Osteoporosis [MeSH] OR Bone Density [MeSH] OR osteoporosis [TIAB] OR bone density [TIAB] OR bone mineral density [TIAB] OR bone mineral content [TIAB] OR bone loss [TIAB] OR bone losses [TIAB] OR bone mineral contents [TIAB] OR osteopenia [TIAB] OR bone mineral densities [TIAB] OR bone densities [TIAB]) AND (Metals, Heavy [MeSH] OR metals, heavy [TIAB] OR Cadmium [MeSH] OR cadmium [TIAB] OR Mercury [MeSH] OR mercury [TIAB] OR Lead [MeSH] OR lead [TIAB]). No limitations for language were imposed. The search strategy for grey literature consisted of the manual search of all original articles cited in the retrieved review articles.

### Inclusion and exclusion criteria

Inclusion criteria were observational studies on adults (≥ 18 years) that provided information about the relationship between heavy metals exposure and the risk of osteopenia or osteoporosis and reported odds ratios (OR) and 95% confidence intervals (CI) of the risk of osteopenia or osteoporosis. Exclusion criteria were studies on children and adolescents (< 18 years); letters, conference reports, case reports, or reviews; and studies where sufficient information was not provided for data reporting, after contacting their corresponding authors. All discrepancies and disagreement about the inclusion and exclusion of studies were resolved by consensus or discussion.

### Study selection

The titles and abstracts of all records were screened for irrelevant records by three investigators, independently (S.M. and C.J.), followed by the full-text review of all relevant records to include eligible studies. We used a standardized approach to apply the inclusion and exclusion criteria that accounted for the design, population, and evaluated exposure(s) and

outcome(s) of induvial studies across the three reviewers (S.M., C.J., and A.H.). All discrepancies and disagreement about the selection of studies were resolved by consensus or discussion.

### Data extraction

Two investigators (S.M. and C.J.) independently extracted data using a standardized approach by Microsoft Office Excel to describe the general characteristics of each study. Accordingly, the first author's name; year of study publication; country and design of the study; number, age, gender, and body mass index (BMI) of study participants; follow-up duration in cohort studies; methods for evaluating exposure to heavy metals; study main findings; and covariates used for adjustment analyses in estimating OR were recorded. All discrepancies and disagreement about data extraction were resolved by consensus or discussion with a third reviewer (H.M.)

### Quality assessment

Two reviewers (S.M. and A.B.) assessed the quality of each study using the Newcastle-Ottawa scale that was adapted for cross-sectional and longitudinal studies [32], where a maximum of ten stars was rewarded to each study. The method of quality assessment has been described previously [33]. The results of the quality assessment for each study are presented in Table 1.

### Data synthesis and statistical analyses

Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA) or SPSS version 25.0 (IBM, Armonk, NY, USA). Data of included studies that reported odds ratios (OR) for heavy metals exposure and the risk of osteopenia or osteoporosis were pooled for meta-analyses. Effect sizes were expressed as pooled OR and 95% confidence intervals (CI) and were estimated using a weighted random-effects model using the DerSimonian-Laird approach [34]. Heterogeneity among the studies was assessed by the Cochran Q and $I^2$ statistics. The $I^2$ value was calculated as ([Q-df])/Q × 100%, Q being the $\chi^2$ value and df the corresponding degree of freedom. The heterogeneity was considered significant where the Q statistics were significant ($P < 0.01$) or $I^2 > 50\%$. No, moderate, high, and extreme heterogeneity were defined according to the cut-offs of < 25%, 25–50%, 50–75%, and > 75%, respectively, using $I^2$ statistics. Sensitivity analysis was performed by removing each study from the analyses and recalculating the pooled effect estimates. We performed $\alpha$ *priori* subgroup analyses to determine any potential impacts of participants' age (18–65 and > 65 years), sex (men, women, and mixed), and the method of exposure assessment (blood, urinary, or dietary levels) on the relationship between exposures and outcomes. Publication bias was assessed by the visual inspection of funnel plots and formal testing by Egger's regression asymmetry and Begg's rank correlation tests [35, 36] and results were considered significant at $P < 0.05$.

## Results

### Study characteristics

The systematic search resulted in 2825 records (Fig. 1) of which 14 records were deemed eligible for and were included in the present work for the qualitative and quantitative assessment [22, 37–50]. General characteristics of included studies are described in Table 1 and are summarized herein. Of all included studies, 13 had a cross-sectional [22, 37–48, 50] and one has a longitudinal design [49]. The studies were published between 2002 and 2018 and were conducted in the USA [46], China [22, 39, 45, 50], Belgium [49], South Korea [38, 40, 41, 43, 44, 47], Sweden [37, 42], and Taiwan [48]. The quality assessment for studies was completed using the Newcastle-Ottawa scale [32] and showed that 13 of included studies had high quality [41–46, 48–50] whereas one had medium quality [47].

The study-specific, maximally adjusted OR were reported for 15,421 individuals across the included studies and were pooled for meta-analysis to examine the associations between heavy metals exposure and the risk of osteopenia or osteoporosis. Of all included studies, 12 reported the effects of cadmium [22, 37–42, 44–47, 49], five reported lead [40, 44, 46, 48, 50], and four reported mercury [40, 43, 44, 46] as their exposure factors.

#### Cadmium exposure and osteopenia or osteoporosis risk

Cadmium exposure was associated with an increased risk of osteopenia or osteoporosis (OR = 1.35; 95% CI: 1.17 to 1.56; $P < 0.001$; Fig. 2). An extreme degree of heterogeneity was observed among the evaluated studies ($I^2$ = 88.6%, $P < 0.001$). Table 2 shows the results of subgroup analyses performed to evaluate any potential effects of age, sex, and method of exposure assessment on these associations. Results of the subgroup analyses by age showed that cadmium exposure was associated with an increased risk of osteopenia or osteoporosis in older adults (> 65 years; OR = 1.43; 95% CI: 1.08 to 1.88, $I^2$ = 92.6%, $P = 0.011$) when compared with all adults (18–65 years; OR = 1.29; 95% CI: 1.12 to 1.48, $I^2$ = 69.8%, $P = 0.03$). Further, results of the subgroup analyses by sex demonstrated that cadmium exposure was associated with an increased risk of osteopenia or

**Table 1** General characteristics of included studies

| Author (year) | Database, design, country | Subjects (age [year]; BMI [kg/m$^2$]; sample size; sex) | Method of exposure assessment (blood, urine, diet) | Follow-up | Main findings | Adjusted variables | Quality Score |
|---|---|---|---|---|---|---|---|
| Alfvén et al. (2002) | OSCAR (osteoporosis-cadmium as a risk factor), cross-sectional, Sweden | Age, 16–81; BMI, NR; $N = 1021$; women and men | Blood Cd | – | Decreased blood levels of Cd were associated with an increased risk of osteoporosis | Age, sex, and smoking status | +8/10 |
| Shin et al. (2011) | Cross-sectional, South Korea | Age, ≥ 18; BMI, NR; $N = 804$; women and men | Urinary Cd | – | Increased urinary levels of Cd were associated with increased risks of osteopenia and osteoporosis | None | +7/10 |
| Cho et al. (2012) | Korean Ministry of Health and Welfare, cross-sectional South Korea | Age, 62.1 ± 8.2; BMI, 24.4 ± 3.3; $N = 481$; women | Blood Cd, Pb, and Hg and arsenic | – | Increased blood levels of Hg were associated with a decreased risk of osteoporosis | Age, BMI, smoking status, alcohol intake, exercise levels, oral contraceptive use, hormone therapy, energy intake, dietary intake of Ca, fish consumption, and vitamin D levels | +9/10 |
| Engström et al. (2012) | Swedish Mammography Cohort (SMC), cross-sectional, Sweden | Age, 64 ± 3.1; BMI, 24 ± 3.4; $N = 2676$; women | Dietary Cd | – | Increased dietary intake of Cd was associated with decreased BMD and an increased risk of osteoporosis | Age, BMI, smoking status, alcohol intake, education status, postmenopausal hormone use, physical activity levels, the status of joint inflammatory disease, and dietary intakes of Ca, Mg, Fe, and fiber | +9/10 |
| Pollack et al. (2013) | BioCycle Study, cross-sectional, USA | Age, 27.4 ± 8.2; BMI, 24.1 ± 3.9; $N = 248$; women | Blood Cd, Pb, and Hg | – | Hg was associated with reduced odds of decreased lumbar spine BMD, but overall, metals at environmentally relevant levels of exposure were not associated with reduced BMD in this population of healthy, reproductive aged women | Age, age at menarche, race, parity, and energy intake | +9/10 |
| Chen et al. (2014) | Cross-sectional, China | Age, ≥ 27; BMI, NR; $N = 321$; women and men | Blood Cd and Pb and urinary Cd | – | Increased blood levels of Cd in women and Pb in men were associated with decreased BMD | Age, weight, height, smoking status, alcohol intake, and menopause status in women. Cd models were further adjusted for Pb exposure, and Pb models were adjusted for Cd exposure | +9/10 |
| Burm et al. (2015) | Korea National Health and Nutrition Examination Survey (KNHANES IV; 2007–2009), cross-sectional, South Korea | Age, 40.3 ± 0.3; BMI, 24.2 ± 0.1; $N = 1275$; women and men | Blood Cd | – | Increased blood levels of Cd were associated with decreased BMD | Age, BMI, height, household income, alcohol intake, hypertension status, diabetes mellitus status, exercise levels, and urinary cotinine | +9/10 |
| Choi et al. (2015) | Korea National Health and Nutrition Examination Survey (KNHANES IV-V; 2008–2011), cross--sectional, South Korea | Age, 58.8 ± 7.5; BMI, NR; $N = 1089$; men | Blood Cd | – | Increased blood levels of Cd were associated with decreased BMD in obese men | Age, BMI, serum creatinine, vitamin D deficiency status, smoking status, alcohol intake, and physical activity levels | +9/10 |
| Tsai et al. (2015) | Nutrition and Health Survey in Taiwan (NAHSIT), cross-sectional, Taiwan | Age, ≥ 18; BMI, 23.8 ± 3.2; | Urinary Pb | – | Increased urinary levels of Pb were associated with reduced risk of decreased BMD | Age, sex, BMI, household income, smoking status, alcohol intake, menopausal status, and U-Cd levels | +9/10 |

**Table 1** (continued)

| Author (year) | Database, design, country | Subjects (age [year]; BMI [kg/m$^2$]; sample size; sex) | Method of exposure assessment (blood, urine, diet) | Follow-up | Main findings | Adjusted variables | Quality Score |
|---|---|---|---|---|---|---|---|
| | | $N = 398$; women and men | | | | | |
| Van Larebeke et al. (2015) | Flemish Environment and Health Survey (FLEHS), prospective study, Belgium | Age, 57.4; BMI, 26.9; $N = 1583$; women and men | Urinary Cd | 7 year | Increased urinary levels of Cd were associated with a decreased risk of osteoporosis | BMI, education status, and exercise level | +9/10 |
| Kim et al. (2016) | Korean National Health and Nutrition Examination Survey (KNHANES; 2008–2010), cross-sectional, South Korea | Age, 61.1 ± 0.2; BMI, 23.8 ± 0.4; $N = 1190$; men | Blood Hg | – | Increased blood levels of Hg were associated with a decreased risk of reduced BMD at the femoral neck level | Age, BMI, alcohol intake, smoking status, exercise level, intake of caloric energy and calcium, fish consumption, and vitamin D level in addition to the corrections included in mode | +9/10 |
| Lim et al. (2016) | Korean National Health and Nutrition Examination Survey (KNHANES; 2008–2011), cross-sectional, South Korea | Age, ≥ 18; BMI, NR; $N = 2429$; women and men | Blood Cd, Pb, and Hg | – | Increased blood levels of Pb and Cd were associated with decreased BMD | Age, sex, lifestyle behaviors (smoking status, alcohol intake, and living region), and sociodemographic factors (education, occupation, and income) | +9/10 |
| Lv et al. (2017) | Cross-sectional, China | Age, 56.4 ± 8.8; BMI, 22.5 ± 3.1; $N = 1116$; women and men | Blood Cd | – | Increased blood levels of Pb and Cd were associated with decreased BMD and an increased risk of osteoporosis | Age, sex, BMI, serum albumin, urinary Ca, and U-Alb | +8/10 |
| Chen et al. (2018) | Cross-sectional China | Age, 53.1 ± 13.0; BMI, NR; $N = 790$; women and men | Dietary Cd | – | Increased dietary intake of Cd was associated with a decreased risk of osteoporosis only in women | Age, weight, height, smoking status, alcohol intake, and menopausal status (women) | +9/10 |

*BMI* body mass index, *BMD* bone mineral density, *Ca* calcium, *Cd* cadmium, *Fe* iron, *Hg* mercury, *NR* not reported, *Mg* magnesium, *Pb* lead, *U-Alb* urinary albumin, U-Cd urinary cadmium

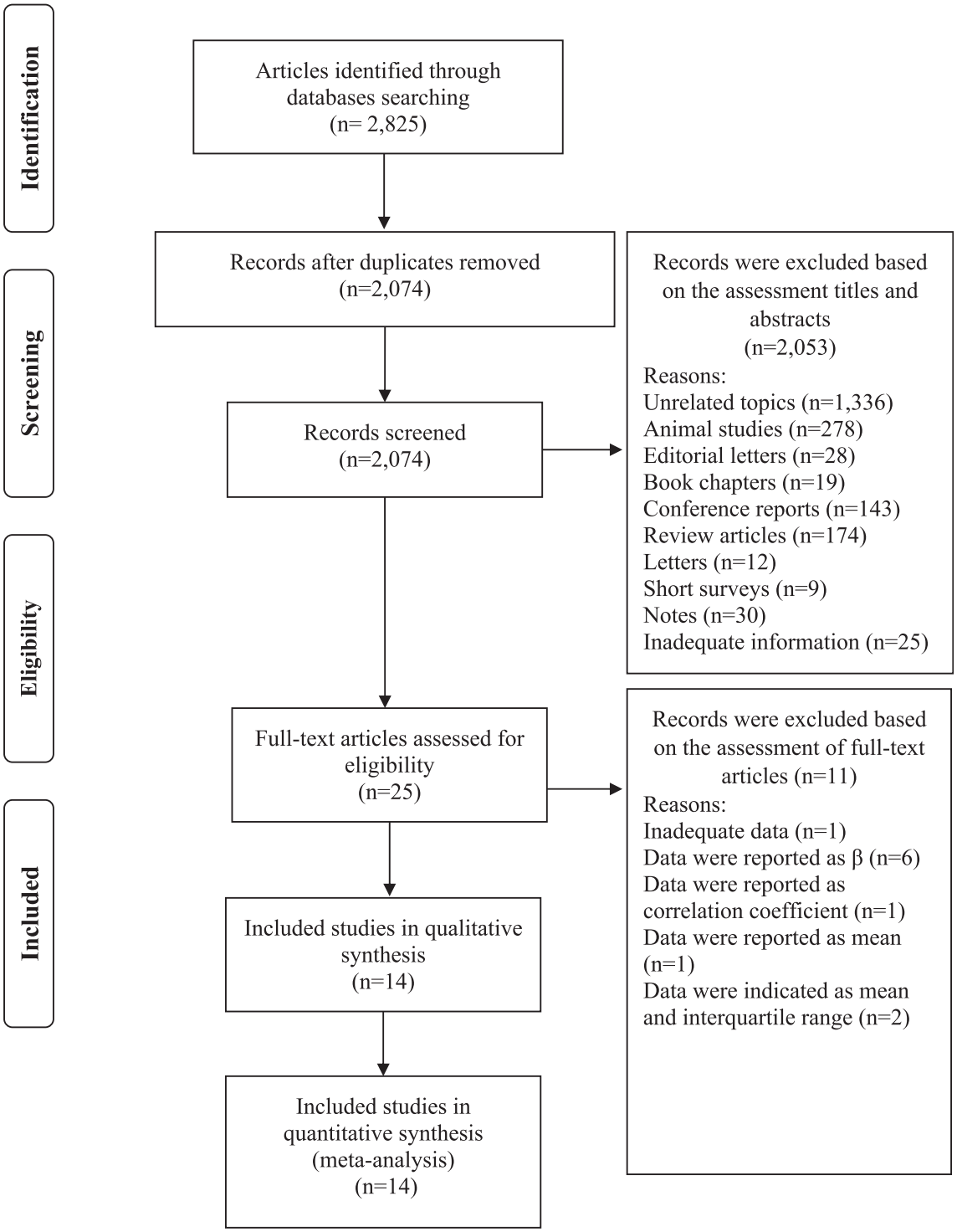


**Fig. 1** Flow chart of the process of the study selection

osteoporosis in both women (OR = 1.21; 95% CI: 1.03 to 1. 42, $I^2$ = 68.2%, $P$ = 0.017) and men (OR = 1.47; 95% CI: 1.04 to 2.07, $I^2$ = 50.0%, $P$ = 0.031). Ultimately, subgroup analyses by the method of exposure assessment revealed that, unlike urinary levels (OR = 1.12; 95% CI: 0.89 to 1.41, $I^2$ = 65.9%, $P$ = 0.337), blood (OR = 1.26; 95% CI: 1.08 to 1.47, $I^2$ = 90.0%, $P$ = 0.003) and dietary levels (OR = 1.46; 95% CI: 1.28 to 1.67, $I^2$ = 0.0%, $P$ < 0.001) of cadmium were associated with an risk of osteopenia or osteoporosis (Table 2).

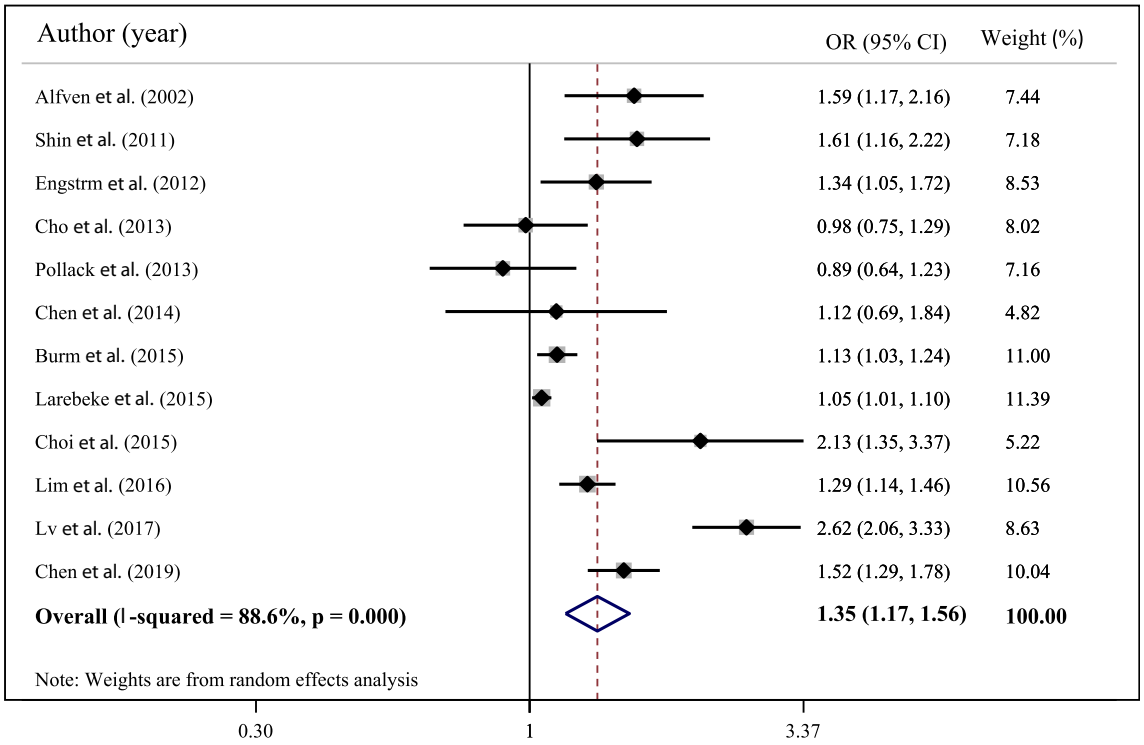


**Fig. 2** Forest plots demonstrating OR and 95% CI of pooled results from the random effects models to evaluate the relationship between cadmium exposure and risk of osteopenia/osteoporosis. OR odds ratio, CI confidence interval

**Table 2** Subgroup analysis to assess the association between heavy metal exposure and risk of osteopenia/osteoporosis

| Subgrouped by | Number of studies | OR[1] | 95% CI | *P* within group | $I^2$ (%) | *P* for heterogeneity |
|---|---|---|---|---|---|---|
| Cadmium exposure | | | | | | |
| Age (years) | | | | | | |
| > 65 | 6 | 1.43 | 1.08–1.88 | 0.011 | 92.6 | < 0.001 |
| 18–65 | 4 | 1.24 | 1.02–1.52 | 0.035 | 75.8 | 0.002 |
| Sex | | | | | | |
| Women | 7 | 1.21 | 1.03–1.42 | 0.017 | 68.2 | 0.004 |
| Men | 4 | 1.47 | 1.04–2.07 | 0.031 | 50.0 | 0.11 |
| Mixed | 5 | 1.40 | 1.14–1.71 | 0.001 | 93.9 | < 0.001 |
| Method of exposure assessment | | | | | | |
| Blood levels | 9 | 1.26 | 1.08–1.47 | 0.003 | 90.0 | < 0.001 |
| Urinary levels | 4 | 1.12 | 0.89–1.41 | 0.337 | 65.9 | 0.03 |
| Dietary levels | 2 | 1.46 | 1.28–1.67 | < 0.001 | 0.0 | 0.41 |
| Lead exposure | | | | | | |
| Sex | | | | | | |
| Women | 4 | 1.16 | 0.95–1.41 | 0.149 | 64.4 | 0.04 |
| Men | 2 | 1.55 | 1.15–2.09 | 0.007 | 26.0 | 0.24 |
| Mixed | 2 | 1.25 | 1.06–1.46 | 0.004 | 28.3 | 0.23 |

*CI* confidence interval, *OR* odds ratio

[1] Calculated by random-effects model

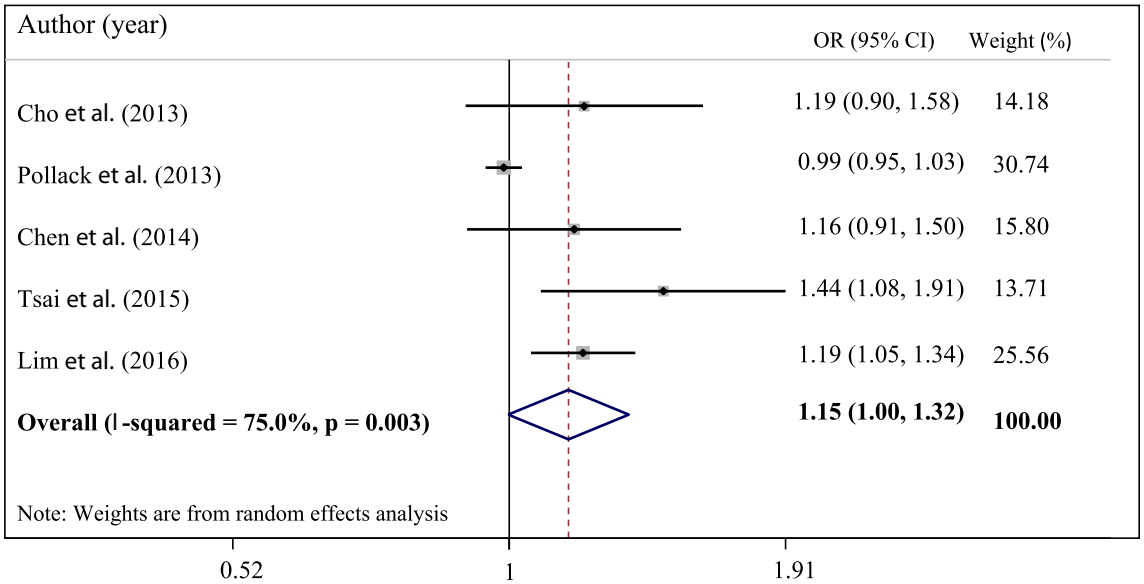


**Fig. 3** Forest plots demonstrating OR and 95% CI of pooled results from the random effects models to evaluate the relationship between lead exposure risk the of osteopenia o osteoporosis. OR odds ratio, CI confidence interval

### Lead exposure and osteopenia or osteoporosis risk

Lead exposure was associated with an increased risk of osteopenia or osteoporosis (OR = 1.15; 95% CI: 1.00 to 1.32; $P = 0.05$; Fig. 3). A high degree of heterogeneity was observed among the studies ($I^2 = 75.0\%$, $P = 0.003$). Results of subgroup analyses by sex showed that lead exposure increased the risk of osteopenia or osteoporosis in men (OR = 1.55; 95% CI: 1.15 to 2.09, $I^2 = 26.0\%$, $P = 0.007$) unlike women (OR = 1.16; 95% CI: 0.95 to 1.41, $I^2 = 64.4\%$, $P = 0.14$; Table 2). Subgroup analyses by sex decreased heterogeneity levels among the evaluated studies (data not shown). We did not perform any further subgroup analyses given the small number of available studies.

### Mercury exposure and osteopenia or osteoporosis risk

We observed no significant associations between mercury exposure and the risk of osteopenia or osteoporosis (OR = 0.85; 95% CI: 0.68 to 1.06, $P = 0.14$). A high degree of heterogeneity was observed among studies ($I^2 = 78.1\%$, $P = 0.003$; Fig. 4). However, we were unable to conduct subgroup analyses to identify potential sources of heterogeneity given the small number of studies.

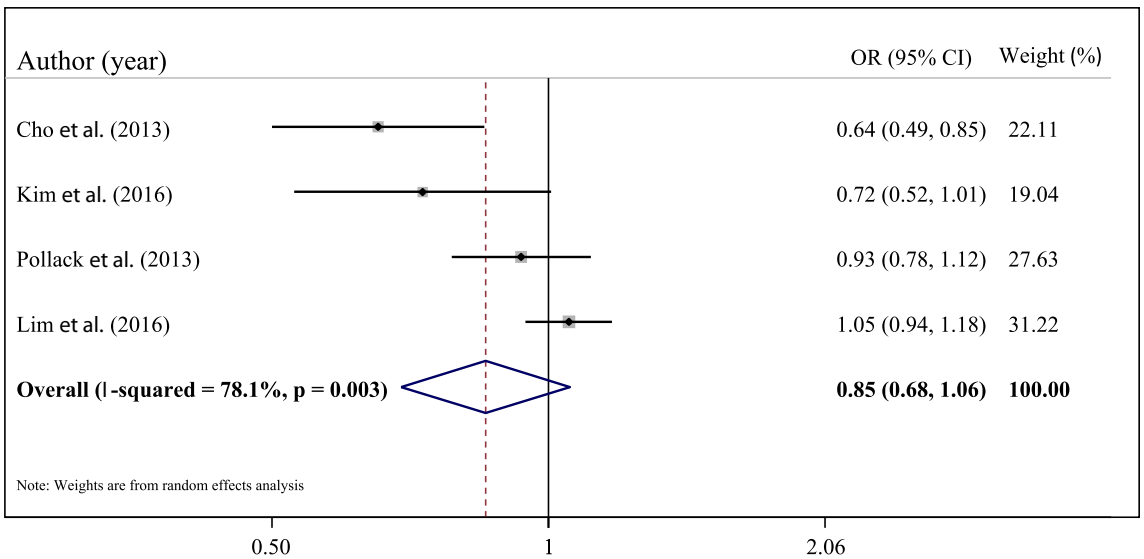


**Fig. 4** Forest plots demonstrating OR and 95% CI of pooled results from the random effects models to evaluate the relationship between mercury exposure and risk of osteopenia/osteoporosis. OR odds ratio, CI confidence interval

### Sensitivity analyses and publication bias

Results of the sensitivity analyses revealed that our observations were not affected by any of the individual studies evaluated. However, the result of the Egger's test showed a publication bias for studies examining associations between cadmium ($P = 0.03$) and lead ($P = 0.04$) exposure and the risk of osteopenia or osteoporosis, albeit these results were not significant as judged by the Begg's test for both cadmium ($P = 0.68$) and lead ($P = 0.32$). There was no evidence of publication bias for studies assessing the associations between mercury exposure and the risk of osteopenia or osteoporosis as evidenced by the results of the Begg's ($P = 0.17$) and Egger's ($P = 0.05$) tests. Similarly, visual inspections of symmetrical funnel plots may indicate no to low evidence of publication bias in studies that evaluated the relationship between exposure to these heavy metals and the risk of osteopenia or osteoporosis (Supplementary Figures 1 and 2).

## Discussion

The present study evaluated the link between exposure to cadmium, lead, and mercury and the risk of osteopenia or osteoporosis. Our finding revealed that exposure to cadmium and lead, but not mercury, is associated with an increased risk of osteopenia or osteoporosis in adults. Older adults and men appear to exhibit an increased risk of osteopenia or osteoporosis in response to exposure to cadmium and lead when compared with younger adults and women, respectively. Further, unlike urinary assessment, blood and dietary assessment captured associations between exposure to cadmium and the likelihood of osteopenia or osteoporosis. Our observations highlight the adverse effects of heavy metals exposure on bone health and reiterate the importance of preventive measures to minimize exposure to heavy metals as environmental contaminants.

Our observations revealed a link between cadmium exposure and the risk of osteopenia or osteoporosis. The biological mechanisms through which cadmium exposure can increase the risk of osteopenia or osteoporosis are complex and not fully understood. Excessive cadmium exposure has been proposed to compromise bone health by decreasing the production of the active form of vitamin D, calcitriol (1,25-dihydroxycholecalciferol); decreasing bone calcium uptake; increasing calcium release into the bloodstream by breaking down the collagen matrix in the bone; interfering with the mineralization of the bone cells; inhibiting the activity of osteoblasts; stimulating the activity of osteoclasts; and altering the expression of genes involved in bone homeostasis [25, 39]. Cadmium exposure may also induce pro-inflammation, generation of reactive oxygen species and oxidative stress, and malnutrition secondary to the malabsorption of essential nutrients [51, 52], all of which are implicated in the pathology of osteopenia and osteoporosis [25, 53–55]. Also, cadmium has been shown to downregulate the expression of key adipokines, including leptin and adiponectin, that are important to maintain bone homeostasis [52], thereby exacerbating bone loss [56, 57].

Our observations of increased risk of osteopenia or osteoporosis in the elderly individuals who were exposed to cadmium may be explained by the biological half-life of the heavy metal. Cadmium has a long (15–30 years) half-life and can be chronically accumulated in the human body [58, 59]. Therefore, it is plausible to conclude that older adults who have a longer exposure time to cadmium would exhibit a higher risk of osteopenia or osteoporosis, albeit we also acknowledge the potential effects of aging and associated comorbidities on compromised bone health [60, 61]. Biomonitoring of cadmium exposure is usually assessed by urinary and blood levels and dietary intake. We observed that, unlike urinary assessment, blood and dietary assessment reflected the relationship between exposure to cadmium and the risk of osteopenia or osteoporosis. A lack of association between the urinary levels of cadmium and risk of osteopenia or osteoporosis may be, in part, due to the small number of studies that were included in the subgroup analyses. Further, the urinary level of cadmium may be a less sensitive and specific marker that is influenced by confounders including age, gender, and diuresis [58] and reflects an exposure over a more extended period when compared to blood levels [59].

In the current study, we showed that exposure to lead increases the risk of osteopenia or osteoporosis. Several mechanisms have been proposed through which lead exposure can compromise bone health. Similar to cadmium, lead has a long (~ 20 years) half-life [62–64] and can be deposited in the liver, kidneys, heart, brain, muscle, and bone [48]. However, the bones contain approximately 95% of total lead in the human body [65, 66]. Exposure to lead induces bone demineralization and bone resorption [67]. Also, lead inhibits the function of chondrocytes and osteoblasts and induces osteoblastic apoptosis, thereby altering many aspects of bone cell formation [21, 68]. Elevated lead concentrations into the bloodstream, secondary to bone resorption, can also negatively affect bone metabolism by interfering with the calcium and phosphorous homeostasis in the kidney through pre-established mechanisms [69]. Also, lead can substitute for divalent trace metals, including calcium ($Ca^{2+}$), zinc ($Zn^{2+}$), magnesium ($Mg^{2+}$), and iron ($Fe^{2+}$) as a second messenger in several ion-dependent events that may affect skeletal development and regulation of bone mass [70]. In our subgroup analysis, we observed that exposure to lead increased the risk of osteopenia or osteoporosis in men, unlike in women. We hypothesized that higher blood lead concentrations in men in our study compared with women would have enabled us to capture these associations. Our observations align with previous reports

about exposure to lead in men and increased risk of osteopenia or osteoporosis [50]. However, our observations may be interpreted with caution due to the small number of included studies in the male subgroup.

We observed no associations between mercury exposure and the risk of osteopenia or osteoporosis. Our observations corroborate those of Pollack et al. about a lack of relationship between mercury exposure and bone health [46]. The lack of associations may be explained by the small number of individual studies available for our analyses, high heterogeneity between the studies, and conflicting results reported by individual studies. It is important to acknowledge that current evidence has suggested both a protective and detrimental role for mercury on bone health [23, 46]. At present, little can be concluded about the effects of mercury exposure on the risk of osteopenia and osteoporosis, and further research is warranted.

### Strengths and limitations

To our knowledge, the present work is the first meta-analysis to summarize the relationship between exposure to cadmium, lead, and mercury and the risk of osteopenia or osteoporosis. We performed a comprehensive search of published literature and adhered to the PRISMA guidelines for reporting our observations. Most of the evaluated studies in the current review had high quality. We used conservative statistical approaches and included sensitivity and subgroup analyses to detect any impact of age, gender, and method of exposure on the overall effect estimates. However, our study had some limitations. We observed high heterogeneity among the included studies, which was maintained even after subgroup and sensitivity analyses, albeit not uncommon in studies of this type. A majority of evaluated studies in the present work focused on exposure to cadmium per se when compared with lead or mercury, which may have decreased our ability to capture any true effects of exposure to lead and mercury on the risk of osteopenia or osteoporosis. Further, any effects of confounding factors, including lifestyle behaviors (diet, smoking, physical activity levels), medication use, and other underlying conditions besides compromised bone health on the risk of osteopenia or osteoporosis were poorly characterized in individual studies; therefore, our results may be interpreted with caution. Additionally, we were unable to evaluate the clinical consequences of osteoporosis associated with exposure to heavy metals including fracture risk given the small number of available studies. Ultimately, there was variability across the individual studies in their methods to assess exposure to heavy metals, including dietary, blood, and urinary assessment, albeit we subgrouped studies to account for the potential impacts of exposure assessment.

## Conclusions

Exposure to cadmium and lead is associated with an increased risk of osteopenia or osteoporosis in adults, which translates into the detrimental effects of select heavy metals, as environmental toxins, on bone health. However, longitudinal high-quality research is required to confirm these observations. Future research should focus to elucidate (1) the biological mechanisms underpinning the relationship between heavy metals exposure and the development of osteopenia or osteoporosis; and (2) the link between heavy metals and bone composition in segmental regions (e.g., femur, pelvis, or spine, especially in the lumbar area) and markers of bone turnover (e.g., osteocalcin) and fracture risk to prevent and manage the negative effects of exposure to heavy metals on bone health.

### Compliance with ethical standards

**Conflicts of interest** None.

## References


1. Black DM, Rosen CJ (2016) Postmenopausal osteoporosis. N Engl J Med 374:254–262
2. Kawalkar AC (2015) A comprehensive review on osteoporosis. J Trauma 10:3–12
3. Moradi S, Shab-bidar S, Alizadeh S, Djafarian K (2017) Association between sleep duration and osteoporosis risk in middle-aged and elderly women: a systematic review and meta-analysis of observational studies. Metabolism 69:199–206
4. Sözen T, Özışık L, Başaran NÇ (2017) An overview and management of osteoporosis. Eur J Rheumatol 4:46–56
5. Pietschmann P, Rauner M, Sipos W, Kerschan-Schindl K (2009) Osteoporosis: an age-related and gender-specific disease–a mini-review. Gerontology 55:3–12
6. Moradi S, Khorrami-Nezhad L, MAGHBOOLI Z, Hosseini B, Keshavarz SA, Mirzaei K (2017) Vitamin D receptor gene variation, dietary intake and bone mineral density in obese women: a cross sectional study. J Nutr Sci Vitaminol 63:228–236
7. Giusti A, Bianchi G (2015) Treatment of primary osteoporosis in men. Clin Interv Aging 10:105
8. Sforza E, Saint Martin M, Thomas T, Collet P, Garet M, Barthélémy JC, Roche F (2016) Risk factors of osteoporosis in healthy elderly with unrecognized obstructive sleep apnea: role of physical activity. Sleep Med 22:25–32
9. Moradi S, Khorrami-nezhad L, Ali-akbar S, Zare F, Alipour T, Bozorg ADK, Yekaninejad MS, Maghbooli Z, Mirzaei K (2018) The associations between dietary patterns and bone health, according to the TGF-β1 T869→ C polymorphism, in postmenopausal Iranian women. Aging Clin Exp Res 30:563–571
10. Guo J-L, Qu C, Bai F, Ma J-H, Chai Y-F (2013) Relations between alcoholism and osteoporosis or femoral head necrosis. Zhonghua liu xing bing xue za zhi 34:732–735
11. Moradi S, Mirzaei K, Abdurahman A, Keshavarz S (2017) Adipokines may mediate the relationship between resting metabolic rates and bone mineral densities in obese women. Osteoporos Int 28:1619–1629
12. Papanikou M, Kotsopoulou A (2014) Osteoporosis and somatization of anxiety. Procedia Soc Behav Sci 113:54–61

13. Christos KF, Maria PE, Ioanna PV, Polina P, Ioannis K, Sofia D, Evangelos F, Lamprini K (2015) Smoking is associated with osteoporosis development in primary care population. Am J Nurs 4:96–101
14. Bolton JM, Morin SN, Majumdar SR, Sareen J, Lix LM, Johansson H, Odén A, McCloskey EV, Kanis JA, Leslie WD (2017) Association of mental disorders and related medication use with risk for major osteoporotic fractures. JAMA Psychiatry 74:641–648
15. Callan AC, Devine A, Qi L, Ng JC, Hinwood AL (2015) Investigation of the relationship between low environmental exposure to metals and bone mineral density, bone resorption and renal function. Int J Hyg Environ Health 218:444–451
16. Bjorklund G, Pivina L, Dadar M, Semenova Y, Aaseth J (2019) Long-term accumulation of metals in the skeleton as related to osteoporotic derangements. Curr Med Chem 26
17. Rai PK, Lee SS, Zhang M, Tsang YF, Kim K-H (2019) Heavy metals in food crops: health risks, fate, mechanisms, and management. Environ Int 125:365–385
18. Anetor J, Babalola O, Alonge T, Adeniyi FA (2019) Bone metabolism in occupational lead toxicity: implications for polluted environments in developing countries. NISEB J 1
19. Bulka CM, Persky VW, Daviglus ML, Durazo-Arvizu RA, Argos M (2019) Multiple metal exposures and metabolic syndrome: a cross-sectional analysis of the National Health and Nutrition Examination Survey 2011–2014. Environ Res 168:397–405
20. Lavado-Garcia JM, Puerto-Parejo LM, Roncero-Martin R, Moran JM, Pedrera-Zamorano JD, Aliaga IJ, Leal-Hernandez O, Canal-Macias ML (2017) Dietary intake of cadmium, lead and mercury and its association with bone health in healthy premenopausal women. Int J Environ Res Public Health 14
21. Campbell JR, Auinger P (2007) The association between blood lead levels and osteoporosis among adults–results from the third national health and nutrition examination survey (NHANES III). Environ Health Perspect 115:1018–1022
22. Chen X, Zhu GY, Jin TY, Wang ZQ (2013) Effects of cadmium on bone mineral density in the distal and proximal forearm: two female population studies in China. Biol Trace Elem Res 156:45–48
23. Kim YH, Shim JY, Seo MS, Yim HJ, Cho MR (2016) Relationship between blood mercury concentration and bone mineral density in Korean men in the 2008-2010 Korean National Health and Nutrition Examination Survey. Kor J Fam Med 37:273–278
24. Puerto-Parejo LM, Aliaga I, Canal-Macias ML, Leal-Hernandez O, Roncero-Martin R, Rico-Martin S, Moran JM (2017) Evaluation of the dietary intake of cadmium, lead and mercury and its relationship with bone health among postmenopausal women in Spain. Int J Environ Res Public Health 14
25. Kazantzis G (2004) Cadmium, osteoporosis and calcium metabolism. Biometals 17:493–498
26. Moran J, Lopez-Arza L, Lavado-Garcia J, Pedrera-Canal M, Rey-Sanchez P, Rodriguez-Velasco F, Fernandez P, Pedrera-Zamorano J (2013) Hormonal relationships to bone mass in elderly Spanish men as influenced by dietary calcium and vitamin D. Nutrients 5:4924–4937
27. Dermience M, Lognay G, Mathieu F, Goyens P (2015) Effects of thirty elements on bone metabolism. J Trace Elem Med Biol 32:86–106
28. Dowd T, Rosen J, Mints L, Gundberg C (2001) The effect of Pb2+ on the structure and hydroxyapatite binding properties of osteocalcin. Biochim Biophys Acta (BBA)-Mol Basis Dis 1535:153–163
29. Yachiguchi K, Sekiguchi T, Nakano M, Hattori A, Yamamoto M, Kitamura KI, Maeda M, Tabuchi Y, Kondo T, Kamauchi H, Nakabayashi H, Srivastav AK, Hayakawa K, Sakamoto T, Suzuki N (2014) Effects of inorganic mercury and methylmercury on osteoclasts and osteoblasts in the scales of the marine teleost as a model system of bone. Zool Sci 31:330–337
30. Suzuki N, Yamamoto M, Watanabe K, Kambegawa A, Hattori A (2004) Both mercury and cadmium directly influence calcium homeostasis resulting from the suppression of scale bone cells: the scale is a good model for the evaluation of heavy metals in bone metabolism. J Bone Miner Metab 22:439–446
31. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clin Res ed) 339:b2700
32. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, Perruolo E, Parati G (2016) Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS One 11:e0147601
33. Moradi S, Mirzababaei A, Dadfarma A, Rezaei S, Mohammadi H, Jannat B, Mirzaei K (2019) Food insecurity and adult weight abnormality risk: a systematic review and meta-analysis. Eur J Nutr 58:45–61
34. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
35. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
36. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315:629–634
37. Alfven T, Jarup L, Elinder CG (2002) Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. Environ Health Perspect 110:699–702
38. Burm E, Ha M, Kwon HJ (2015) Association between blood cadmium level and bone mineral density reduction modified by renal function in young and middle-aged men. J Trace Elem Med Biol 32:60–65
39. Chen X, Wang Z, Zhu G, Nordberg GF, Jin T, Ding X (2019) The association between cumulative cadmium intake and osteoporosis and risk of fracture in a Chinese population. J Expos Sci Environ Epidemiol 29:435–443
40. Cho GJ, Park HT, Shin JH, Hur JY, Kim SH, Lee KW, Kim T (2012) The relationship between blood mercury level and osteoporosis in postmenopausal women. Menopause (New York, NY) 19:576–581
41. Choi WJ, Han SH (2015) Blood cadmium is associated with osteoporosis in obese males but not in non-obese males: the Korea National Health and Nutrition Examination Survey 2008–2011. Int J Environ Res Public Health 12:12144–12157
42. Engström A, Michaëlsson K, Vahter M, Julin B, Wolk A, Åkesson A (2012) Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. Bone 50:1372–1378
43. Kim YD, Eom SY, Yim DH, Kim IS, Won HK, Park CH, Kim GB, Yu SD, Choi BS, Park JD, Kim H (2016) Environmental exposure to arsenic, lead, and cadmium in people living near Janghang copper smelter in Korea. J Korean Med Sci 31:489–496
44. Lim HS, Lee HH, Kim TH, Lee BR (2016) Relationship between heavy metal exposure and bone mineral density in Korean adult. J Bone Metab 23:223–231
45. Lv YJ, Wang P, Huang R, Liang X, Wang P, Tan J, Chen Z, Dun Z, Wang J, Jiang Q, Wu S, Ling H, Li Z, Yang X (2017) Cadmium exposure and osteoporosis: a population-based study and benchmark dose estimation in southern China. J Bone Miner Res 32:1990–2000
46. Pollack AZ, Mumford SL, Wactawski-Wende J, Yeung E, Mendola P, Mattison DR, Schisterman EF (2013) Bone mineral density and blood metals in premenopausal women. Environ Res 120:76–81
47. Shin M, Paek D, Yoon C (2011) The relationship between the bone mineral density and urinary cadmium concentration of residents in an industrial complex. Environ Res 111:101–109

48. Tsai TL, Pan WH, Chung YT, Wu TN, Tseng YC, Liou SH, Wang SL (2016) Association between urinary lead and bone health in a general population from Taiwan. J Expos Sci Environ Epidemiol 26:481–487
49. Van Larebeke N, Sioen I, Hond ED, Nelen V, Van de Mieroop E, Nawrot T, Bruckers L, Schoeters G, Baeyens W (2015) Internal exposure to organochlorine pollutants and cadmium and self-reported health status: a prospective study. Int J Hyg Environ Health 218:232–245
50. Chen X, Wang K, Wang Z, Gan C, He P, Liang Y, Jin T, Zhu G (2014) Effects of lead and cadmium co-exposure on bone mineral density in a Chinese population. Bone 63:76–80
51. Hsu C-W, Lin J-L, Lin-Tan D-T, Yen T-H, Huang W-H, Ho T-C, Huang Y-L, Yeh L-M, Huang L-M (2008) Association of environmental cadmium exposure with inflammation and malnutrition in maintenance haemodialysis patients. Nephrol Dial Transplant 24: 1282–1288
52. Kawakami T, Nishiyama K, Kadota Y, Sato M, Inoue M, Suzuki S (2013) Cadmium modulates adipocyte functions in metallothionein-null mice. Toxicol Appl Pharmacol 272:625–636
53. Hsu C-W, Lin J-L, Lin-Tan D-T, Huang W-H, Chen K-H, Yen T-H (2014) Association between blood cadmium levels and malnutrition in peritoneal dialysis. BMC Nephrol 15:17
54. Wätjen W, Beyersmann D (2004) Cadmium-induced apoptosis in C6 glioma cells: influence of oxidative stress. Biometals 17:65–78
55. Mundy GR (2007) Osteoporosis and inflammation. Nutr Rev 65: S147–S151
56. Cervellati C, Bonaccorsi G, Bergamini CM, Fila E, Greco P, Valacchi G, Massari L, Gonelli A, Tisato V (2016) Association between circulatory levels of adipokines and bone mineral density in postmenopausal women. Menopause (New York, NY) 23:984–992
57. Upadhyay J, Farr OM, Mantzoros CS (2015) The role of leptin in regulating bone metabolism. Metabolism 64:105–113
58. Akerstrom M, Barregard L, Lundh T, Sallsten G (2014) Variability of urinary cadmium excretion in spot urine samples, first morning voids, and 24 h urine in a healthy non-smoking population: implications for study design. J Expo Sci Environ Epidemiol 24:171–179
59. Wang Q, Wei S (2018) Cadmium affects blood pressure and negatively interacts with obesity: findings from NHANES 1999–2014. Sci Total Environ 643:270–276
60. Bonewald L (2019) Use it or lose it to age: a review of bone and muscle communication. Bone 120:212–218
61. Delaney MF (2006) Strategies for the prevention and treatment of osteoporosis during early postmenopause. Am J Obstet Gynecol 194:S12–S23
62. Bergdahl IA, Strömberg U, Gerhardsson L, Schütz A, Chettle DR, Skerfving S (1998) Lead concentrations in tibial and calcaneal bone in relation to the history of occupational lead exposure. Scand J Work Environ Health 24:38–45
63. Gerhardsson L, Attewell R, Chettle D, Englyst V, Lundström N, Nordberg G, Nyhlin H, Scott M, Todd A (1993) In vivo measurements of lead in bone in long-term exposed lead smelter workers. Arch Environ Health 48:147–156
64. Suwazono Y, Kido T, Nakagawa H, Nishijo M, Honda R, Kobayashi E, Dochi M, Nogawa K (2009) Biological half-life of cadmium in the urine of inhabitants after cessation of cadmium exposure. Biomarkers 14:77–81
65. Barry PS (1975) A comparison of concentrations of lead in human tissues. Br J Ind Med 32:119–139
66. Barry PS, Mossman DB (1970) Lead concentrations in human tissues. Br J Ind Med 27:339–351
67. Silbergeld EK, Schwartz J, Mahaffey K (1988) Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ Res 47:79–94
68. Rodríguez J, Mandalunis PM (2018) A review of metal exposure and its effects on bone health. J Toxicol 2018:1–11
69. Sauk JJ, Somerman MJ (1991) Physiology of bone: mineral compartment proteins as candidates for environmental perturbation by lead. Environ Health Perspect 91:9–16
70. Pounds JG, Long GJ, Rosen JF (1991) Cellular and molecular toxicity of lead in bone. Environ Health Perspect 91:17–32